(TRANSLATION)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA220) as well as, what applicable, item 5 below.
TOK-8		
International application No.	International Filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/JP99/06166	05. 11. 99	05. 11. 98
Applicant: Toyama Chemical Co., Ltd.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report
   a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless other wise indicated under this item.
      ☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
   b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:
      ☐ contained in the international application in written form.
      ☐ filed together with the international application in computer readable form.
      ☐ furnished subsequently to this Authority in written form.
      ☐ furnished subsequently to this Authority in computer readable form.
      ☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
      ☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.
2. ☒ Certain claims were found unsearchable (See Box I).
3. ☐ Unity of invention is lacking (See Box II).
4. With regard to the title,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established by this Authority to read as follows:
5. With regard to the abstract,
   ☒ the text is approved as submitted by the applicant.
   ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is Figure No. ———
   ☐ as suggested by the applicant.
   ☐ because the applicant failed to suggest a figure.
   ☐ because this figure better characterizes the invention.
   ☒ None of the figures

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP99/06166

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 31
because they relate to subject matter not required to be searched by this Authority, namely:

The subject matter of claim 31 relates to a method for treatment of the human body by therapy, which does not require an international search report by the International Search Authority in accordance with PCT Article 17(2) (a)(i) and Rule 39.1(iv).

2. ☒ Claims Nos.: 1-4
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

See Extra Sheet.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP99/06166

Continuation of Box I Observation where certain claims were found unsearchable

Claim 31 pertains to methods for treatment of the human body by therapy and thus relates to a subject matter which this International Searching Authority is not required, under the provisions of Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.

The compound as set forth in claim 1 is specified exclusively by the following two requirements:

(1) having an atom corresponding to a hydrogen bond acceptor atom in a hydrogen bond acceptor group and at least two atoms corresponding to at least two atoms selected from among an atom to which a donor hydrogen atom in a hydrogen bond donor group is bonded or a hydrogen bond acceptor atom in a hydrogen bond acceptor group and three arbitrary carbon atoms constituting a hydrophobic group, among five atoms constituting a pharmacophore; and

(2) in the optimized stereochemical structure of the compound, the atoms of the compound having specific interatomic distances.

However, no particular element is described therein as the atom corresponding to the hydrogen bond acceptor atom in the hydrogen bond acceptor group and the atom to which the donor hydrogen atom in the hydrogen donor group is bonded in the above requirement (1). Also, no particular chemical structure is specified with respect to the hydrogen bond acceptor group, the hydrogen bond donor group and the hydrophobic group. Moreover, neither particular element as the atoms corresponding to these atoms nor relation among them is stated therein. In addition, it is impossible merely on the basis of the above (2) to understand which compounds can satisfy these requirements.

A really existing compound has a chemical structure represented by, for example, a chemical structural formula. In case of a hypothetical compound, it seems possible to calculate interatomic distances among the atoms constituting the compound on the basis of the optimized chemical structure thereof. However, it is difficult or impossible to define a compound in detail merely based on the interatomic distances merely among atoms of elements which have not been specified.

Moreover, it is not stated in the description of the present case how to understand particular compounds based on the requirements (1) and (2) as described above.

It is therefore impossible to understand the compound as set forth in claim 1 as a chemical.

In claim 2, the interatomic distances among the atoms constituting the pharmacophore are specified merely in a narrower scope. Therefore, the compound cannot be understood as a chemical too.

Although the atoms constituting the pharmacophore are selectively described in claim 3, it is not stated therein which atoms correspond thereto. Further, the relation among the interatomic distances stated therein is same as in claim 1. Therefore, the compound cannot be understood as a chemical too.

In claim 4, it is specified that the compound has an effect of antagonistically inhibiting the binding of AP-1 to the recognition sequence. However, it still remains difficult to immediately understand the compound, even though this specification is taken into consideration. Therefore, the compound cannot be understood as a chemical too.

Such being the case, it is unavoidable to conclude that requirements of claims 1 to 4 are not stated in the description, claims or drawings to such an extent as ensuring effective International Searching, or that the description is considerably unclear.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP99/06166

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] C07C69/73, 69/767, 205/49, 229/00, 233/01, 251/32, 255/49, 311/02, 317/00, 321/24, C07K7/06, C07D207/08, 207/10, 207/32, 209/18, 209/42, 213/30, 213/64, 235/26, 241/08, 277/60, 401/14, A61K31/18, 31/216, 31/277, 31/40, 31/415, 31/428, 31/44, 31/495, 38/08, A61P19/02, 37/06, 43/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] C07C69/73, 69/767, 205/49, 229/00, 233/01, 251/32, 255/49, 311/02, 317/00, 321/24, C07K7/06, C07D207/08, 207/10, 207/32, 209/18, 209/42, 213/30, 213/64, 235/26, 241/08, 277/60, 401/14, A61K31/18, 31/216, 31/277, 31/40, 31/415, 31/428, 31/44, 31/495, 38/08, A61P19/02, 37/06, 43/00
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS(STN), CAOLD(STN), REGISTRY(STN)
BIOSIS(STN), MEDLINE(STN), WPIDS(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP, 10-130201, A (EISAI CO., LTD., Mercian Corporation), 19 May, 1998 (19.05.98) (Family: none)	5-30,32-34
A	JP, 10-36272, A (Toyama Chemical Co., Ltd.), 10 February, 1998 (10.02.98) (Family: none)	5-30,32-34
Y	GLOVER, J. N. Mark & HARRISON, Stephen C., "Crystal structure of the heterodimeric bZIP transcription factor c-Fos-c-Jun bound to DNA", Nature, 1995, Vol.373, No.6511, p.257-p.261	5-30,32-34
Y	NISHIBATA, Yoshihiko & ITAI, Akiko, "Automatic Creation of Drug Candidate Structures Based on Receptor Structure. Starting Point for Artificial Lead Generation", Tetrahedron, 1991, Vol.47, No.43, p.8985-p.8990	5-30,32-34
Y	MARTIN, Yvonne C., "3D Database Searching in Drug Design", Journal of Medicinal Chemistry, 1992, Vol.35, No.12, p.2145-p.2154	5-30,32-34
A	WO, 96/40189, A1 (GLAXO GROUP LIMITED), 19 December, 1996 (19.12.96)	5-8

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 January, 2000 (25.01.00)	08 February, 2000 (08.02.00)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP99/06166

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	& AU, 9660466, A1	
A	YAO, Shao et al., "Uncoiling c-Jun coiled coils: inhibitory effects of truncated Fos peptides on Jun dimerization and DNA binding in vitro", Biopolymers, 1998, Vol.47, No.4, p.277-p.283	5-8,29,30, 32-34
A	EP, 150166, A1 (PHARMACIA AB), 31 July, 1985 (31.07.85) & WO, 85/3287, A1 & AU, 574129, B & JP, 61-500915, A & US, 4695648, A	9-11,16-21,28
X	CUSHMAN, Mark et al., "New Alkenyldiarylmethanes with Enhanced Potencies as Anti-HIV Agents Which Act as	16
Y	Non-Nucleoside Reverse Transcriptase Inhibitors", Journal of Medicinal Chemistry, 1998, Vol.41, No.12, p.2076-p.2089	5-30,32-34
X	NEAMATI, Nouri et al., "Depsides and Depsidones as Inhibitors of HIV-1 Integrase: Discovery of Novel	16
Y	Inhibitorsthrough 3D Database Searching", Journal of Medicinal Chemistry, 1997, Vol.40, No.6, p.942-p.951	5-30,32-34
X	CUSHMAN, Mark et al., "Inhibition of HIV-1 integration protein by aurintricarboxylic acid monomers, monomer	16
A	analogs, and polymer fractions", Biochem. Biophys. Res. Commun., 1992, Vol.185, No.1, p.85-p.90; especially, p.86 Scheme 7	17
X	EP, 639573, A1 (Hoechst Aktiengesellschaft), 22 February, 1995 (22.02.95), especially, page 29, Beispiel I/6 & DE, 4326005, A1 & DE, 4414316, A1	24

WO 00/27792
PCT/JP99/06166

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
TOYAMA CHEMICAL CO., LTD.
2-5, Nishishinjuku 3-chome
Shinjuku-ku, Tokyo 160-0023
JAPON

Date of mailing (day/month/year) 18 May 2000 (18.05.00)	
Applicant's or agent's file reference TOK-8	**IMPORTANT NOTICE**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/JP99/06166	05 November 1999 (05.11.99)	05 November 1998 (05.11.98)

Applicant
TOYAMA CHEMICAL CO., LTD. et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,CN,KP,KR,MA,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CR,CU,CZ,DE,DK,DM,EA,EE,EP,ES,FI,GB,GD,GE,
   GH,GM,HR,HU,ID,IL,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,OA,
   PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,UZ,VN,YU,ZA,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   18 May 2000 (18.05.00) under No. WO 00/27792

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, **a demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

TOYAMA CHEMICAL CO., LTD.
2-5, Nishishinjuku 3-chome
Shinjuku-Ku, Tokyo 160-0023
JAPON

Date of mailing (day/month/year) 20 January 2000 (20.01.00)	
Applicant's or agent's file reference TOK-8	**IMPORTANT NOTIFICATION**
International application No. PCT/JP99/06166	International filing date (day/month/year) 05 November 1999 (05.11.99)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 05 November 1998 (05.11.98)
Applicant TOYAMA CHEMICAL CO., LTD. et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).

2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.

3. An **asterisk(*)** appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The **letters "NR"** appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
05 Nove 1998 (05.11.98)	10/328792	JP	06 Janu 2000 (06.01.00)
25 Marc 1999 (25.03.99)	11/80693	JP	06 Janu 2000 (06.01.00)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

F. Zotomayor

Telephone No. (41-22) 338.83.38

m.H

特 許 協 力 条 [redacted]

EP US PCT

国際調査報告

（法８条、法施行規則第40、41条）
〔ＰＣＴ１８条、ＰＣＴ規則43、44〕

出願人又は代理人の書類記号　ＴＯＫ－８	今後の手続きについては、国際調査報告の送付通知様式（ＰＣＴ／ＩＳＡ／２２０）及び下記５を参照すること。	
国際出願番号 ＰＣＴ／ＪＰ９９／０６１６６	国際出願日 （日.月.年）　０５．１１．９９	優先日 （日.月.年）　０５．１１．９８
出願人（氏名又は名称） 富山化学工業株式会社		

国際調査機関が作成したこの国際調査報告を法施行規則第41条（ＰＣＴ１８条）の規定に従い出願人に送付する。
この写しは国際事務局にも送付される。

この国際調査報告は、全部で　5　ページである。

☐ この調査報告に引用された先行技術文献の写しも添付されている。

１．国際調査報告の基礎

ａ．言語は、下記に示す場合を除くほか、この国際出願がされたものに基づき国際調査を行った。
☐ この国際調査機関に提出された国際出願の翻訳文に基づき国際調査を行った。

ｂ．この国際出願は、ヌクレオチド又はアミノ酸配列を含んでおり、次の配列表に基づき国際調査を行った。
☐ この国際出願に含まれる書面による配列表
☐ この国際出願と共に提出されたフレキシブルディスクによる配列表
☐ 出願後に、この国際調査機関に提出された書面による配列表
☐ 出願後に、この国際調査機関に提出されたフレキシブルディスクによる配列表
☐ 出願後に提出した書面による配列表が出願時における国際出願の開示の範囲を超える事項を含まない旨の陳述書の提出があった。
☐ 書面による配列表に記載した配列とフレキシブルディスクによる配列表に記録した配列が同一である旨の陳述書の提出があった。

２．☒ 請求の範囲の一部の調査ができない（第Ⅰ欄参照）。

３．☐ 発明の単一性が欠如している（第Ⅱ欄参照）。

４．発明の名称は
☒ 出願人が提出したものを承認する。
☐ 次に示すように国際調査機関が作成した。

５．要約は
☒ 出願人が提出したものを承認する。
☐ 第Ⅲ欄に示されているように、法施行規則第47条（ＰＣＴ規則38.2(b)）の規定により国際調査機関が作成した。出願人は、この国際調査報告の発送の日から１カ月以内にこの国際調査機関に意見を提出することができる。

６．要約書とともに公表される図は、
第＿＿＿＿図とする。☐ 出願人が示したとおりである。　☒ なし
☐ 出願人は図を示さなかった。
☐ 本図は発明の特徴を一層よく表している。

国際調査報告

国際出願番号　ＰＣＴ／ＪＰ９９／０６１６６

第Ⅰ欄　請求の範囲の一部の調査ができないときの意見（第１ページの２の続き）

法第８条第３項（ＰＣＴ１７条(2)(a)）の規定により、この国際調査報告は次の理由により請求の範囲の一部について作成しなかった。

1．☒ 請求の範囲 ＿＿＿３１＿＿＿ は、この国際調査機関が調査をすることを要しない対象に係るものである。つまり、

請求の範囲３１は、人の身体の治療による処置に関するものであるから、ＰＣＴ１７条(2)(a)(i)及びＰＣＴ規則 39.1(iv)の規定により、この国際調査機関が調査をすることを要しない対象に係るものである。

2．☒ 請求の範囲 ＿＿＿１－４＿＿＿ は、有意義な国際調査をすることができる程度まで所定の要件を満たしていない国際出願の部分に係るものである。つまり、

別紙（特別ページ）参照。

3．☐ 請求の範囲 ＿＿＿＿＿＿＿＿＿＿ は、従属請求の範囲であってＰＣＴ規則6.4(a)の第２文及び第３文の規定に従って記載されていない。

第Ⅱ欄　発明の単一性が欠如しているときの意見（第１ページの３の続き）

次に述べるようにこの国際出願に二以上の発明があるとこの国際調査機関は認めた。

1．☐ 出願人が必要な追加調査手数料をすべて期間内に納付したので、この国際調査報告は、すべての調査可能な請求の範囲について作成した。

2．☐ 追加調査手数料を要求するまでもなく、すべての調査可能な請求の範囲について調査することができたので、追加調査手数料の納付を求めなかった。

3．☐ 出願人が必要な追加調査手数料を一部のみしか期間内に納付しなかったので、この国際調査報告は、手数料の納付のあった次の請求の範囲のみについて作成した。

4．☐ 出願人が必要な追加調査手数料を期間内に納付しなかったので、この国際調査報告は、請求の範囲の最初に記載されている発明に係る次の請求の範囲について作成した。

追加調査手数料の異議の申立てに関する注意

☐ 追加調査手数料の納付と共に出願人から異議申立てがあった。

☐ 追加調査手数料の納付と共に出願人から異議申立てがなかった。

国際調査報告

国際出願番号　PCT／JP99／06166

A.　発明の属する分野の分類（国際特許分類（IPC））

Int. Cl' C07C69/73, 69/767, 205/49, 229/00, 233/01, 251/32, 255/49, 311/02, 317/00, 321/24, C07K7/06, C07D207/08, 207/10, 207/32, 209/18, 209/42, 213/30, 213/64, 235/26, 241/08, 277/60, 401/14, A61K31/18, 31/216, 31/277, 31/40, 31/415, 31/428, 31/44, 31/495, 38/08, A61P19/02, 37/06, 43/00

B.　調査を行った分野

調査を行った最小限資料（国際特許分類（IPC））

Int. Cl' C07C69/73, 69/767, 205/49, 229/00, 233/01, 251/32, 255/49, 311/02, 317/00, 321/24, C07K7/06, C07D207/08, 207/10, 207/32, 209/18, 209/42, 213/30, 213/64, 235/26, 241/08, 277/60, 401/14, A61K31/18, 31/216, 31/277, 31/40, 31/415, 31/428, 31/44, 31/495, 38/08, A61P19/02, 37/06, 43/00

最小限資料以外の資料で調査を行った分野に含まれるもの

国際調査で使用した電子データベース（データベースの名称、調査に使用した用語）

CAPLUS (STN)、CAOLD (STN)、REGISTRY (STN)
BIOSIS (STN)、MEDLINE (STN)、WPIDS (STN)

C.　関連すると認められる文献

引用文献のカテゴリー＊	引用文献名　及び一部の箇所が関連するときは、その関連する箇所の表示	関連する請求の範囲の番号
A	JP, 10-130201, A (エーザイ株式会社、メルシャン株式会社) 19. 5月. 1998 (19. 05. 98) (ファミリーなし)	5～30, 32～34
A	JP, 10-36272, A (富山化学工業株式会社) 10. 2月. 1998 (10. 02. 98) (ファミリーなし)	5～30, 32～34
Y	GLOVER, J. N. Mark & HARRISON, Stephen C., "Crystal structure of the heterodimeric bZIP transcription factor c-Fos-c-Jun bound to DNA", Nature, 1995, Vol. 373, No. 6511, p. 257-p. 261	5～30, 32～34

☒ C欄の続きにも文献が列挙されている。　☐ パテントファミリーに関する別紙を参照。

＊　引用文献のカテゴリー
「A」特に関連のある文献ではなく、一般的技術水準を示すもの
「E」国際出願日前の出願または特許であるが、国際出願日以後に公表されたもの
「L」優先権主張に疑義を提起する文献又は他の文献の発行日若しくは他の特別な理由を確立するために引用する文献（理由を付す）
「O」口頭による開示、使用、展示等に言及する文献
「P」国際出願日前で、かつ優先権の主張の基礎となる出願の日の後に公表された文献
「T」国際出願日又は優先日後に公表された文献であって出願と矛盾するものではなく、発明の原理又は理論の理解のために引用するもの
「X」特に関連のある文献であって、当該文献のみで発明の新規性又は進歩性がないと考えられるもの
「Y」特に関連のある文献であって、当該文献と他の1以上の文献との、当業者にとって自明である組合せによって進歩性がないと考えられるもの
「&」同一パテントファミリー文献

国際調査を完了した日	国際調査報告の発送日
25. 01. 00	08.02.00

国際調査機関の名称及びあて先	特許庁審査官（権限のある職員）	
日本国特許庁（ISA／JP） 郵便番号100-8915 東京都千代田区霞が関三丁目4番3号	藤森　知郎	4H　9357
	電話番号　03-3581-1101　内線　3443	

様式PCT／ISA／210（第2ページ）（1998年7月）

C（続き）．　関連すると認められる文献

引用文献のカテゴリー＊	引用文献名　及び一部の箇所が関連するときは、その関連する箇所の表示	関連する請求の範囲の番号
Y	NISHIBATA, Yoshihiko & ITAI, Akiko, "Automatic Creation of Drug Candidate Structures Based on Receptor Structure. Starting Point for Artificial Lead Generation", Tetrahedron, 1991, Vol.47, No.43, p.8985-p.8990	5～30, 32～34
Y	MARTIN, Yvonne C., "3D Database Searching in Drug Design", Journal of Medicinal Chemistry, 1992, Vol.35, No.12, p.2145-p.2154	5～30, 32～34
A	WO, 96／40189, A1 (GLAXO GROUP LIMITED) 19.12月.1996 (19.12.96) & AU, 9660466, A1	5～8
A	YAO, Shao et al., "Uncoiling c-Jun coiled coils: inhibitory effects of truncated Fos peptides on Jun dimerization and DNA binding in vitro", Biopolymers, 1998, Vol.47, No.4, p.277-p.283	5～8, 29, 30, 32～34
A	EP, 150166, A1 (PHARMACIA AB) 31.7月.1985 (31.07.85) & WO, 85／3287, A1 & AU, 574129, B & JP, 61－500915, A & US, 4695648, A	9～11, 16～21, 28
X	CUSHMAN, Mark et al., "New Alkenyldiarylmethanes with Enhanced Potencies as Anti-HIV Agents Which Act as	16
Y	Non-Nucleoside Reverse Transcriptase Inhibitors", Journal of Medicinal Chemistry, 1998, Vol.41, No.12, p.2076-p.2089	5～30, 32～34
X	NEAMATI, Nouri et al., "Depsides and Depsidones as Inhibitors of HIV-1 Integrase: Discovery of Novel Inhibitors	16
Y	through 3D Database Searching", Journal of Medicinal Chemistry, 1997, Vol.40, No.6, p.942-p.951	5～30, 32～34
X	CUSHMAN, Mark et al., "Inhibition of HIV-1 integration protein by aurintricarboxylic acid monomers, monomer	16
A	analogs, and polymer fractions", Biochem. Biophys. Res. Commun., 1992, Vol.185, No.1, p.85-p.90 特に p.86 Scheme 7	17
X	EP, 639573, A1 (Hoechst Aktiengesellschaft) 22.2月.1995 (22.02.95) 特に第29頁 Beispiel I/6 & DE, 4326005, A1 & DE, 4414316, A1	24

第Ⅰ欄　請求の範囲の一部の調査ができないときの意見　2．の続き

請求の範囲１の化合物は、
（1）ファーマコフォーを構成する５つの原子のうち、水素結合受容基中の水素結合受容原子に対応する原子１つと、１つの水素結合供与基中の供与性水素原子が結合した原子もしくは水素結合受容基中の水素結合受容原子および３つの疎水性基を構成する任意の炭素原子から選択される２つ以上の原子に対応する原子２つ以上を有すること、
および
（2）その化合物が最適化された立体構造において、上記化合物の有する原子が特定の原子間距離を有すること、
の二つの要件のみで特定されている。

しかしながら、上記（1）において水素結合受容基中の水素結合受容原子に対応する原子および水素結合供与基中の供与性水素原子が結合した原子が具体的にどの元素であるか記載されておらず、水素結合受容基、水素結合供与基および疎水性基が具体的にどのような化学構造を有するものであるのかも特定されていない。また、これらの原子に対応する原子が具体的にどの元素であるか、その対応関係も記載されていない。さらに、上記（2）の条件だけからは、具体的にどのような化合物群がかかる要件を満たすものであるのかも把握できない。
すなわち、実在する化合物は化学構造式等によって表現される化学構造を有しており、ある化合物を仮定すれば、その化学構造に基づいて、最適化された立体構造において、化合物を構成する原子が互いにどのような原子間距離にあるかを計算することも可能であるとは認められる。しかしながら、化合物を構成する一部の、しかも元素が特定されていない原子同士の原子間距離だけから直ちに、それが具体的にどのような化合物であるのかを把握することは極めて困難ないし不可能である。
しかも、本出願の明細書を参照しても、上記（1）および（2）の要件から、具体的な化合物をどのように把握することができるのかも記載されていない。
したがって、請求の範囲１の化合物を化学物質として把握することができない。

また、請求の範囲２は、ファーマコフォーを構成する原子の原子間距離がより狭い範囲に特定されているにすぎず、同様に化合物を化学物質として把握することができない。

請求の範囲３は、ファーマコフォーを構成する原子が選択的に記載されているが、この原子に対応する原子が何であるか記載されておらず、また、互いの原子間の関係も請求の範囲１と同じであるから、同様に化合物を化学物質として把握することができない。

請求の範囲４は、化合物がＡＰ－１とその認識配列の結合を拮抗的に阻害する作用を有することが特定されているが、この特定を加えても、具体的な化合物を直ちに把握することは依然として困難であるから、同様に化合物を化学物質として把握することができない。

よって、請求の範囲１～４は、有効な国際調査をすることができる程度に、明細書、請求の範囲もしくは図面に必要な事項が記載されておらず、またはその記載が著しく不明確である、と認めざるを得ない。

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 03 July 2000 (03.07.00)	
International application No. PCT/JP99/06166	**Applicant's or agent's file reference** TOK-8
International filing date (day/month/year) 05 November 1999 (05.11.99)	**Priority date** (day/month/year) 05 November 1998 (05.11.98)
Applicant CHAKI, Hisaaki et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

31 May 2000 (31.05.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Y. KUWAHARA
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference TOK-8	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/JP99/06166	International filing date (*day/month/year*) 05 November 1999 (05.11.99)	Priority date (*day/month/year*) 05 November 1998 (05.11.98)
International Patent Classification (IPC) or national classification and IPC C07C 69/73, 69/767, 205/49, 229/00, 233/01, 251/32, 255/49, 311/02, 317/00, 321/24, C07K 7/06, C07D 207/08, 207/10, 207/32, 209/18, 209/42, 213/30, 213/64, 235/26, 241/08, 277/60, 401/14, A61K 31/18, 31/216, 31/277, 31/40, 31/415, 31/428, 31/44, 31/495, 38/08, A61P 19/02, 37/06, 43/00		
Applicant TOYAMA CHEMICAL CO., LTD.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
31 May 2000 (31.05.00)	22 September 2000 (22.09.2000)
Name and mailing address of the IPEA/JP Facsimile No.	Authorized officer Telephone No.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Front page

Continuation of the International Patent Classification (IPC)

Int. Cl^7 A61K31/18, 31/216, 31/277, 31/40, 31/415, 31/428, 31/44, 31/495, 38/08, A61P19/02, 37/06, 43/00

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/JP99/06166

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:

pages 1-234, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

☒ the claims:

pages 1-15,17-23,25-34, as originally filed

pages _____, as amended (together with any statement under Article 19

pages _____, filed with the demand

pages 16,24, filed with the letter of 18 September 2000 (18.09.2000)

☐ the drawings:

pages _____, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

☐ the sequence listing part of the description:

pages _____, as originally filed

pages _____, filed with the demand

pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-4,31

because:

☒ the said international application, or the said claims Nos. 31
relate to the following subject matter which does not require an international preliminary examination *(specify)*:

See supplemental sheet for continuation of Box III. 1.

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-4
are so unclear that no meaningful opinion could be formed *(specify)*:

See supplemental sheet for continuation of Box III. 1.

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 1-4,31 .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III. 1.

Claim 31 pertains to treatment of the human body by surgery or therapy and thus relates to a subject matter that does not require preliminary examination by this International Preliminary Examination Authority, under the provisions of PCT Article 34(4)(a)(i) and PCT Rule 67.1(iv).

Claims 1-4: See separate sheet (supplemental sheet).

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III. 1.

Non-establishment of an opinion as to novelty, inventive step and applicability. 1. Reason, continued

The compounds disclosed in Claim 1 are defined only by the following two conditions:

(1) having among the 5 atoms constituting the pharmacophore one atom corresponding to a hydrogen bond acceptor atom in a hydrogen bond acceptor group, and at least two atoms corresponding to at least two atoms selected from one atom to which a donor hydrogen atom is bound in a hydrogen bond donor group or a hydrogen bond acceptor atom in a hydrogen bond accepting group and any three constituent carbon atoms of a hydrophobic group; and

(2) in the optimum three-dimensional structure of the compound, specified interatomic distances between atoms of the compound.

However, Claim 1 does not indicate what actual elements can constitute the hydrogen bond acceptor atom in the hydrogen bond acceptor group or the atom to which a donor hydrogen atom is bound in a hydrogen bond donor groups in (1) above, and does not specify actual chemical structures for the hydrogen bond acceptor group, hydrogen bond donor group or hydrophobic group. Nor is it clear what elements are envisaged as the atoms corresponding to these atoms, or the relationship underlying the correspondence. Moreover, from condition (2) alone it is impossible to deduce what actual groups of compounds satisfy said condition.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III. 1.

In other words, although it is recognized that existing compounds have a structure which can be expressed by a structural formula, for example, and it is possible for any given compound to calculate the distances between atoms constituting the compound in an optimized three-dimensional structure on the basis of the chemical structure thereof, it is extremely difficult, if not impossible, to deduce directly from distances between atoms in part of the structure of a compound alone, when the specific elements involved are unclear, what sort of compounds will satisfy this condition.

Moreover, the description of the present application gives no principles or theoretical background to enable a person skilled in the art to deduce specifically what sort of compounds satisfy above conditions (1) and (2) other than the compounds presented as examples.

Therefore, it is impossible to understand the compounds described in Claim 1 as chemical substances.

Claim 2 merely specifies narrower ranges for distances between atoms constituting the pharmacophore, and it is likewise impossible to understand the compounds as chemical substances.

Claim 3 selectively describes the atoms constituting the pharmacophore; however, it remains unclear what elements are envisaged as the atoms corresponding to these atoms or what relationship underlies correspondence, and the relationship among the atoms is as in Claim 1. Therefore, it is likewise impossible to understand the compounds as chemical substances.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III. 1.

Claim 4 specifies that the compounds competitively inhibit AP-1 and binding to the recognition sequence thereof. However specifying the effect of the compounds does not clarify the specific chemical structure thereof, and it remains difficult to identify specific compounds. Therefore, it is likewise impossible to understand the compounds as chemical substances.

Consequently, the description, claims and drawings lack the information necessary to enable international preliminary examination of Claims 1-4, and the disclosure thereof is exceedingly unclear.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	5-30, 32-34	**YES**
	Claims		**NO**
Inventive step (IS)	Claims		**YES**
	Claims	5-30, 32-34	**NO**
Industrial applicability (IA)	Claims	5-30, 32-34	**YES**
	Claims		**NO**

2. Citations and explanations

Document 1: J. N. Mark Glover & Stephen C. Harrison, "Crystal structure of the hetodimeric bZIP transcription factor c-Fos-c-Jun bound to DNA", Nature, 1995, Vol. 373, No. 6511, pp. 257-261

Document 2: Yoshihiko Nishibata & Akiko Itai, "Automatic creation of drug candidate structures based on receptor structure. Starting point for artificial lead generation", Tetrahedron, 1991, Vol. 47, No. 43, pp. 8985-8990

Document 3: Yvonne C. Martin, "3D database searching in drug design", Journal of Medicinal Chemistry, 1992, Vol. 35, No. 12, pp. 2145-2154

Document 4: Mark Cushman et al., "New alkenyldiaryl-methanes with enhanced potencies as anti-HIV agents which act as non-nucleoside reverse transcriptase inhibitors", Journal of Medicinal Chemistry, 1998, Vol. 41, No. 12, pp. 2076-2089

Document 5: Nouri Neamati et al., "Depsides and

depsidones as inhibitors of HIV-1 integrase: discovery of novel inhibitors through 3D database searching", Journal of Medicinal Chemistry, 1997, Vol. 40, No. 6, pp. 942-951

Claims 5-30 and 32-34 do not involve an inventive step in the light of Document 1 and Documents 2-5 cited in the international search report.

As indicated in Document 1, the three-dimensional structure of transcription factor AP-1 is known, and as indicated in Documents 2-5, methods for designing inhibitors, etc., with reference to three-dimensional structures are also known. Moreover, the use of pharmacophore models in designing inhibitors, etc., with reference to three-dimensional structures is also routine in the art.

Therefore, given the three-dimensional structure of AP-1, a person skilled in the art could easily derive compounds which inhibit AP-1, and obtain agents for preventing and treating conditions to which AP-1 contributes.